Moderator’s view: Ambulatory blood pressure monitoring and home blood pressure for the prognosis, diagnosis and treatment of hypertension in dialysis patients

Carmine Zoccali1, Rocco Tripepi1, Claudia Torino1, Giovanni Tripepi1 and Francesca Mallamaci1,2

1CNR-IFC, Clinical Epidemiology and Pathophysiology of Hypertension and Renal Diseases, Ospedali Riuniti, Reggio Calabria, Italy and 2Nephrology, Hypertension and Renal Transplantation Unit, Ospedali Riuniti, Reggio Calabria, Italy

Correspondence and offprint requests to: Carmine Zoccali; E-mail: carmine.zoccali@tin.it

ABSTRACT

Major health agencies now recommend the systematic application of ambulatory blood pressure monitoring (ABPM) for the diagnosis of hypertension. Given the exceedingly high prevalence of nocturnal hypertension, masked and white coat hypertension and the overt inadequacy of peridialysis (pre-, intra- and post-dialysis) BP measurements, more extensive application of ABPM for the diagnosis of hypertension in dialysis patients would appear logical. In a recent survey performed in NDT Educational, organizational problems and/or cognitive resistance emerged as important factors hindering more extensive application of ABPM and home BP by nephrologists. External validation of observations made in landmark studies in a single institution about hypertension subcategorization by ABPM is urgently needed. Furthermore, apparent cognitive resistance by nephrologists may be justified by the fact that these techniques have been insufficiently tested in the dialysis population for applicability in everyday clinical practice, tolerability, organizational impact and cost-effectiveness. We should be more resolute in abandoning peridialysis measurements for diagnosing and treating hypertension in haemodialysis patients. Home BP is a formidable educational instrument for patient empowerment and self-care, and evidence exists that this technique is superior to peridialysis values to better hypertension control as defined on the basis of ABPM. We should strive to promote more extensive application of home BP monitoring to diagnose and manage hypertension in haemodialysis patients. ABPM with novel, user friendly and better tolerated techniques is to be awaited in the near future.

Keywords: ABPM, dialysis, ESRD, home BP, hypertension

INTRODUCTION

Arterial pressure in stage G5D CKD patients is routinely measured peridialysis, i.e. before, during or after dialysis, and current knowledge on the risk of hypertension in this population is largely based on peridialytic measurements. However, it is well established that these metrics do not reflect the actual arterial pressure burden as assessed by the golden standard (ambulatory blood pressure monitoring for 44 h during the dialysis interval) [1]. Pre-dialysis BP overestimates average arterial pressure during the dialysis interval while post-dialysis BP underestimates the same parameter. This issue is further compounded by the high frequency of nocturnal [2] and masked and white-coat hypertension [3] in the dialysis population. Thus, there is a serious risk of hypertension misdiagnosis in haemodialysis patients. In one of the biggest changes to previous guidelines from the National Institute for Health and Clinical Excellence (NICE) in Great Britain, the most recent guideline by the same institute now recommends that in all individuals with a BP >140/90 mmHg or higher during an office visit, ABPM should be proposed [4]. Home blood pressure monitoring can be offered as an alternative for those unable to use ABPM. This move by NICE stimulated a thorough revision of guidelines by scientific societies and led to the establishment of a compelling set of indications for the application of ABPM by an expert committee of the European Society of Hypertension [5] (Table 1), which substantially echoes recommendations by NICE. More recently, based on a meta-analysis funded by the US Agency for Healthcare Research and Quality [6], the American US Preventive Services Task Force has issued a recommendation supporting ABPM. The meta-analysis showed that 5 to 65% of patients with high office blood pressure might not be truly...
hypertensive as defined by ABPM. An ambulatory BP monitor costs about 2000 EU (2250 US$). It was estimated that primary care physicians would need one monitor for every 2000 patients [4], which is the average size of a general practice in most EU countries and in the USA. The cost of the monitor would be amortized in 1 year due to savings in unnecessary treatment and visits [4]. Thus, ABPM is not only useful for the diagnosis of hypertension in the community but also cost-effective. What are the implications of the new guidelines and cost-effectiveness analyses of ABPM for the dialysis population? Even though the issue at stake in this Polar View is ABPM, I will discuss ABPM side by side with home BP monitoring, a simpler and less expensive technique that is proposed as an alternative to ABPM.

CAN WE TAKE FOR GRANTED THAT TREATMENT OF HYPERTENSION IS EVENLY AND SENSIBLY BENEFICIAL IN DIALYSIS PATIENTS?

In the early days of dialysis, when the average age of this population was 46 years and when patients with comorbidities were very often excluded from chronic dialysis programmes, high blood pressure was a direct predictor of mortality and cardiovascular events [10]. In the new millennium, the average age of the dialysis population is approaching 70 years in most economically developed countries, and blood pressure is inversely rather than directly associated with mortality in this population [11], a phenomenon attributed to reverse causality triggered by structural heart disease. Because life expectancy is very low in old dialysis patients, the benefits of hypertension treatment cannot be taken for granted in these patients. Old age, comorbidities and frailty [12] are strong risk factors for complications and adverse effects of interventions. Treatment of hypertension may cause intradialytic hypotension (which is per se a risk factor for death) and orthostatic hypotension and falls while the benefits of lower BP levels on cardiovascular outcomes may not be immediate (see below). In such a dim scenario, the risk of harm may exceed the chances of benefit by the same interventions. Making a reliable diagnosis of hypertension with ABPM or home BP monitoring makes sense only if we are certain that treating hypertension produces tangible health benefits. This line of reasoning surfaces in Alan Jardine’s CON part of this Polar View [13]. Indeed, he remarks that the pattern of cardiovascular disease is unique in this population because heart failure (a long-term sequel of systemic hypertension [14]) and sudden death dominate the scene. He also stresses that in most studies all-cause and cardiovascular mortality were unrelated to BP. A salient point by Alan Jardine is that because BP depends on volume status it is a preferable targeting therapy based on markers of volume status and left ventricular (LV) mass and function rather than on BP. However, the usefulness of this intriguing approach still remains to be proven. The effect on health outcomes of treatment policies guided by volume status and echocardiography has been investigated even less than traditional BP-based policies. Furthermore, the BP burden is a notorious, major effect-or of the long-term detrimental effects of volume overload until severe LV dysfunction supervenes. Reliable knowledge of the BP burden is fundamental in clinical practice in haemodialysis patients.

Table 1. Compelling indications for ABPM (ESH guidelines 2014 [5])

| Identifying white-coat hypertension phenomena |
| White-coat hypertension in untreated individuals |
| White-coat effect in treated or untreated individuals |
| False resistant hypertension due to white-coat effect in treated individuals |
| Identifying masked hypertension phenomena |
| Masked hypertension in untreated individuals |
| Masked uncontrolled hypertension in treated individuals |
| Identifying abnormal 24-h BP patterns |
| Daytime hypertension |
| Siesta dipping/post-prandial hypotension |
| Nocturnal hypertension |
| Dipping status/isolated nocturnal hypertension |
| Assessment of treatment |
| Assessing 24-h BP control |
| Identifying true resistant hypertension |

CAN ABPM AND HOME BP MONITORING CONTRIBUTE TO REFINING THE PROGNOSIS IN DIALYSIS PATIENTS?

ABPM [7] and home BP measurements [8] in dialysis patients are linearly related to the risk of death while office measurements have a complex relationship with the same outcome (see below). However, neither ABPM nor home BP convey meaningful discriminant or reclassification power over and above standard risk factors. In studies performed so far in haemodialysis patients, the independent risk (hazard rate, HR) associated with confirmed (sustained) hypertension (a 44-hour ambulatory BP of \( \geq 135/85 \) mmHg and a median midweek intradialytic BP of \( \geq 140/80 \) mmHg) and for home BP (\( >140/90 \) mmHg) is between 2.0 and 3.0 [7]. In order to add sufficient discriminatory power over and above other risk factors for the identification of patients who will go on to develop future events (death, cardiovascular events) and/or to improve risk classification at an individual level, risk factors should have a very high HR (in general >10) for the outcome of interest [9]. Thus, it can be excluded that ABPM or home BP per se adds meaningful predictive power to standard risk factors in dialysis patients. The same reasoning applies to ABPM application in the general population.

However, the lack of prognostic power of a given risk factor does not exclude that interventions to modify the same risk factor can produce health benefits. Therapy is an issue related to aetiology and risk factor modification rather than to risk prediction. What we expect from these techniques is that they will provide a valid guide for diagnosis and treatment of hypertension in dialysis patients. We already know very well that they play a minimal or no role in risk stratification and prognosis.
The benefits of appropriate diagnosis and treatment of hypertension in high-risk patients demand juxtaposing at an individual level of life expectancy to time needed for the health benefits of antihypertensive treatment (including volume control by ultrafiltration and reduction in salt intake and drug therapy) materialization. Today, the average age of the dialysis population in most European and North American countries is over 60 years and is approaching 70 years. A typical example of today’s dialysis patient is a 68-year-old male with a renal disease of unknown aetiology and a functioning fistula, a smoker with no history of cancer, who had had a myocardial infarction, with serum CRP of 13 mg/dL, serum ferritin 323 mg/dL, BMI 28, creatinine 650 Mol/L (7.35 mg/dL), serum albumin 3.4 mg/dL and calcium 2.3 mMol/L. According to a recent, well-validated risk calculator in the dialysis population [15], the 1-year death probability of this patient is about 15% (the average mortality rate in the ERA-EDTA Registry) which coincides with a life expectancy of 6.6 years (life expectancy 1/mortality). In general, the benefits of cardiovascular therapies appear early on when treatment is applied, but in some studies very long time-lags to cardiovascular benefit (i.e. a late divergence in survival curves between the treatment and the control arm) have been registered. For example, in the ADVANCE study in type-2 diabetics, the time-lag to benefit of antihypertensive drugs ranged from 12 months (all-cause death) to 18 months (cardiovascular events) [16]. Even adopting such a long lag-time if the patient in question (expected survival 6.6 years) has a confirmed diagnosis of hypertension (e.g. hypertension as defined by ABPM or by home BP monitoring), the patient may benefit from antihypertensive treatment. Figure 1 shows that about two-thirds of the dialysis population in Europe has a death risk of 35%/year or less, i.e. a life expectancy of 2.8 years or greater, which gives sufficient time for the cardiovascular benefits of hypertension control to materialize. A recent meta-analysis remarked that the benefits of antihypertensive treatment are evident at all risk levels [17] and that in absolute terms such benefits are even greater in patients with a higher baseline cardiovascular risk, as a tenet remarked 15 years ago in a classic review of the risk of end-stage renal disease by the same cardiovascular epidemiologists [18]. Provided that dialysis patients have a sufficiently long survival, there is no reason to believe that the benefit of treatment be negated to these patients. In a recent analysis in the Chronic Renal Insufficiency Cohort (CRIC), out of dialysis systolic BP measurement predicted a linear increase in the risk of death from 110 mmHg on [19]. Even in a very high-risk condition like heart failure, when standardized BP measurements out of dialysis go down [carvedilol (−9/−8 mmHg) [20] or telmisartan (−7/−5 mmHg) [21]], the risk of death does as well. Thus, streamlining the diagnosis and treatment of hypertension in the dialysis population has relevant potential for improving health outcomes.

In his counter-deductions to the PRO contender [22], it is clear that Alan Jardine agrees that at least home BP measurements, a method investigated by Rajiv Agarwal about 10 years ago [23], are needed for proper diagnosis and management of hypertension in the dialysis population. Home BP costs less and is better accepted by patients. Can home BP measurements surrogate ABPM for the diagnosis of hypertension and for BP targeting in the dialysis population?
Furthermore, the same technique reclassified 42 out of 61 patients with white coat hypertension by home BP (68%) as having true (sustained) hypertension [26]. Importantly, in haemodialysis patients there are no analyses focusing on the contribution of night-time BP values to prevailing 24 or 44-h ABPM average values in the same population. Given the high frequency of non-dipping and nocturnal hypertension in end-stage renal disease, the problem of masked hypertension—the Achilles’ heel of home BP monitoring—may be even more serious than in the general population. A thorough meta-analysis including studies in primary care and in other settings remarked that home BP monitoring has insufficient sensitivity or specificity to be recommended as a single diagnostic test [27]. Taking into account the high prevalence of nocturnal hypertension in dialysis patients, home BP in the dialysis scenario has similar or possibly greater limitations than in other healthcare settings. Notwithstanding being inferior to ABPM in accuracy, the fact remains that home BP is also unquestionably superior to peridialysis measurements for the diagnosis and treatment of hypertension in these patients [28].

**ABPM AND HOME BP IN THE CLINICAL SCENARIO: A SURVEY**

In an NDT Educational survey performed in March–April 2015, 278 nephrologists replied to a short questionnaire about ABPM and home BP monitoring (Figure 2). This sample is hardly representative of the readership of this online resource of the ERA EDTA. Rather, it represents the habits and beliefs of a group of highly motivated nephrologists who keep themselves updated also via this educational WEB site. Thus, the results of this survey should be considered as a very optimistic picture of real clinical practice. About a half of the participants had access to ABPM, which in 68% of cases was a service offered within the same department or directly managed within the renal unit. ABPM was used systematically by just 18% of participants (either for the diagnosis of hypertension or for monitoring therapy) and by an additional 29% only when pre-dialysis BP values were considered too variable. The technique was applied by 8% of nephrologists in patients with a diagnosis of heavy snoring or with overt sleep apnoea. Home BP had no better prospects in that it was used systematically by only 22% of nephrologists (35% resorted to home BP only in doubtful cases). Thus, even the most motivated nephrologists face substantial organizational problems for the application of ABPM or home BP monitoring and/or do not consider these techniques as instruments central for the diagnosis and treatment of hypertension in the dialysis population. The argument has been made that there is a cognitive dissonance and apathy among physicians dealing with hypertensive patients [29]. However, we believe that nephrologists’ resistance to the call of extensive application of ABPM depends on the fact that knowledge about the use of ABPM in haemodialysis patients is still quite limited. Most information gathered so far about hypertension subcategorization by ABPM (masked, white-coat and sustained hypertension) [3] about the validity of home BP monitoring [23] largely derives from studies performed in a single clinical research centre in the USA. External validation is still needed for findings in these careful studies to be considered generalizable and applicable to other centres worldwide. Furthermore, this technique has been insufficiently tested.

**FIGURE 2:** Availability and use of ABPM and home BP monitoring in an NDT educational survey done in April–May 2015. A total of 278 nephrologists (60% Europeans, 5% Americans, 10% Asians and 25% by other countries) participated in this survey.

- ABPM instruments are applied and managed by personnel (technicians or nurses) of the Renal Unit (internal service) 68%
- by other specialists (i.e. by external services, e.g. cardiology) 20%
- *The external ABPM service is efficient and we have no problem 6%*
- *We have relevant problems with for having timely ABPM measurements when needed 6%*
- *systematically and periodically (e.g. once a year or more often) in every patient starting dialysis treatment 18%*
- *rarely for diagnostic purposes or for monitoring antihypertensive treatment 23%*
- *only in patients with variable pre-dialysis BP values 29%*
- *in doubtful cases, never in patients with obvious pre-dialysis hypertension (i.e. average monthly BP >140 syst and or >90 mmHg diastolic) and in those who have pre-dialysis BP levels (≤140/90 mmHg) 30%*
in the dialysis population as to applicability in everyday clinical practice, organizational impact, cost and cost-effectiveness. Organizing an internal service for ABPM in a haemodialysis unit with 60 patients has face-affordability (Box 1). In the analysis made by NICE [30], confirming a diagnosis of hypertension by ABPM instead of office or home BP was the most cost-effective option at all ages, and ABPM cost-effectiveness was corroborated by various sensitivity analyses. The key driver of cost savings was hypertension treatment costs avoided due to more accurate diagnosis (increased specificity). Being that life expectancy is much shorter in dialysis patients than in their peers in the general population, the savings are bound to be less in the dialysis scenario. Specific analyses in dialysis patients, considering the potential gain in quality-adjusted life years, are sorely needed.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest in relationship to the content of this manuscript.


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